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(71) Applicant *(for all designated States except US)*: **NESTEC S.A.** [CH/CH]; Avenue Nestlé 55, CH-1800 Vevey (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **POUTEAU, Etienne** [FR/CH]; Rue de L'Industrie 3, CH-1005 Lausanne (CH). **GARCIA-RODENAS, Clara, Lucia** [ES/CH]; Résidence Le Frêne 3, CH-1072 Forel (Lavaux) (CH). **MACE, Catherine** [FR/CH]; Avenue des Mousquines 27, CH-1005 Lausanne (CH).

(74) Agent: **RAULINE, Mathilde**; Avenue Nestlé 55, CH-1800 Vevey (CH).

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(54) Title: COMPOSITION FOR TREATING AND/OR PREVENTING DYSFUNCTIONS ASSOCIATED WITH TYPE 2 DIABETES MELLITUS AND INSULIN RESISTANCE

(57) Abstract: The present invention relates to the use of a composition for treating, preventing and/or improving metabolic dysfunctions associated with type 2 diabetes mellitus and insulin resistance, said composition comprising acetogenic fibers, and at least one compound selected from the group consisting of intact whey proteins and mixtures of free amino acids, and to nutritional or pharmaceutical compositions and functional food products.

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Composition for treating and/or preventing dysfunctions associated with Type 2 diabetes mellitus and insulin resistance

The present invention relates to the use of a composition comprising acetogenic fibers and at least one compound selected from intact whey protein and a mixture of free amino acids, for treating and/or preventing insulin resistance and/or dysfunctions associated with Type 2 diabetes mellitus, and to nutritional or pharmaceutical compositions and functional food products containing these ingredients.

Diabetes mellitus and insulin resistance both are metabolic disorders exhibiting a major common manifestation, hyperglycaemia.

Diabetes mellitus originates from an inherited and/or acquired deficiency in the production of insulin by the pancreas, and/or by the ineffectiveness of the insulin produced, hepatic and peripheral tissues becoming resistant to insulin action. Such a deficiency in insulin secretion and insulin sensitivity eventually results in increased concentrations of glucose in the blood, which in turn damage many of the body's systems, in particular the blood vessels and nerves.

There are two principle forms of diabetes, Type 1 and Type 2.

In Type 1 diabetes the pancreas of affected individuals fails to produce insulin largely due to a destruction of the islets of Langerhans, which in most cases seem to occur as a consequence of an auto-immune reaction triggered by some environmental factor, such as a viral infection. Heavy lymphocytic infiltrates appear in and around islets with the number and size of islets being reduced, eventually leading to decreased insulin production and glucose intolerance. This form develops most frequently in children and adolescents, but is being increasingly noted later in life.

Type 2 diabetes results from the body's inability to properly respond to the action of insulin

produced by the pancreas. It occurs most frequently in adults, but is being noted increasingly in adolescents as well. The islets of Langerhans are normal in number or somewhat reduced with type II diabetes mellitus. Fibrosis and deposition of amylin polypeptide within islets are most characteristic of the chronic states of Type 2 diabetes.

Diabetes mellitus of both types is associated with a number of life-threatening and/or handicapping diseases. Examples are nodular and diffuse glomerulosclerosis, which may lead to chronic renal failure. Diabetics are prone to infections, particularly pyelonephritis. Also the eyes may be affected with diabetic retinopathy being one of the leading causes for irreversible blindness. Most persons with Type 1 diabetes and many of those with Type 2 diabetes develop some sort of background (non-proliferative) retinopathy. In severe cases, neo-vascularization may lead to adhesions (synechiae) between iris and cornea or iris and lens, eventually leading to secondary glaucoma with blindness. Also cataracts are more common in diabetics. This predilection for development of cataracts is felt to result from hyperglycemia leading to accumulation of sorbitol that results in osmotic damage to the crystalline lens.

Persons with diabetes mellitus, either Type 1 or Type 2, also exhibit early and accelerated atherosclerosis. The most serious complications of this are atherosclerotic heart disease, cerebrovascular disease, and renal disease, with the most common cause of death being myocardial infarction. Peripheral vascular disease is a particular problem with diabetes mellitus and is made worse through the development of diabetic neuropathy, leading to propensity for injury. Mucormycosis is another feared complication in individuals experiencing diabetes mellitus. The site of involvement is typically the nasopharyngeal region, but the infection can spread to involve soft tissues and bone of the face, orbit, skull, and brain.

The treatment of individuals suffering from diabetes generally involves physical activity, diet and/or administration of medicaments. People with Type 1 diabetes are usually totally dependent on insulin injections for survival, requiring daily administration. Type 2 diabetic patients usually have to observe a strict diet and may additionally receive oral anti-

diabetics, such as sulphonyl ureas, alpha-glucosidase inhibitors and biguanides, or even insulin injections, the administration of which is often associated with severe side effects and complications.

The majority of people suffer from Type 2 diabetes, which accounts for around 90% of all diabetes cases world-wide. On the molecular level Type 2 diabetes is characterized by a defect of both, insulin secretion and action. The defect of insulin secretion relates mostly to the first phase of the post-prandial insulin release from pancreas, wherein in diabetic patients the already formed insulin is stored within the β-cells, but cannot be released into circulation. Indeed, most of the Type 2 diabetic patients present a resistance to the action of the insulin such that in order to cope with similar glucose concentration as present in healthy people, Type 2 diabetics require a higher concentration of insulin in plasma.

Another type of abnormality in glucose metabolism is insulin resistance, that is, a reduced sensitivity in the tissues of the body to the action of insulin, which goes along with a perturbed lipid (blood fats) metabolism, obesity, and high blood pressure. This cluster of abnormalities has come to be known as a syndrome, going by a variety of names, including Syndrome X, the Deadly Quartet, and the Insulin Resistance Syndrome.

When insulin resistance, or reduced insulin sensitivity, exists, the body attempts to overcome this resistance by secreting more insulin from the pancreas. The development of Type 2, or non-insulin dependent, diabetes occurs when the pancreas fails to sustain this increased insulin secretion. The importance of the Insulin Resistance Syndrome, or perhaps more accurately, "The Pluri-Metabolic Syndrome", lies in its consequences. The syndrome is typically characterized by varying degrees of glucose intolerance, abnormal cholesterol and/or triglyceride levels, high blood pressure, and upper body obesity, all independent risk factors for cardiac disease.

Following a meal, a person suffering insulin resistance will have elevated glucose circulating in the blood, signalling yet more insulin to be released from the pancreas until the glucose is taken up by the cells. Experts suggest that 11 to 25 percent of the adult

population may be resistant to insulin to some degree.

The use of milk protein hydrolysates to improve glucose metabolism or control glycaemic response in individuals suffering from diabetes has already been suggested in US Patent Application No. 2003/0004095. According to this document, milk protein hydrolysates, specifically caseinoglycomacropeptide can induce the release of GLP-1, a peptide known to be capable of potentiating glucose-induced insulin secretion as well as stimulating proinsulin gene expression and proinsulin biosynthesis. However, milk protein hydrolysates are known to have an unpleasant bitter taste which may adversely affect patient compliance with a regime based on these products.

Due to the increasing number of affected people world-wide and the changing lifestyle of the society there exists a need in the art to provide additional means useful in preventing, treating and/or improving conditions associated with Type 2 diabetes mellitus and/or insulin resistance. Moreover, such a means should be essentially free from disadvantageous side-effects well known from many oral anti-diabetics, and should be easy to take up.

The present invention provides a method of treating, preventing and/or improving metabolic dysfunctions and conditions associated with Type 2 diabetes mellitus or insulin resistance by administering an effective amount of a composition comprising acetogenic fibres, and at least one compound selected from the group consisting of intact whey protein and mixtures of free amino acids.

The invention further extends to a nutritional or pharmaceutical composition comprising acetogenic fibers, intact whey proteins and a mixture of free amino acids, each in an amount in the range of from about 1 to 90 % by weight, preferably from 5 to 70 % by weight, more preferably 11 to 50 % by weight, even more preferably 21 to 40 % by weight, most preferred about 25 to 35 % by weight, based on the total dry weight of the composition.

The invention further provides a method for treating, preventing and/or improving metabolic dysfunctions or conditions associated with Type 2 diabetes mellitus or insulin resistance which comprises administering an effective amount of a composition comprising acetogenic fibres, and at least one compound selected from the group consisting of intact whey proteins and mixtures of free amino acids

During the extensive studies leading to the present invention, it has been found that a composition comprising these essential ingredients enhances post-prandial insulinemia, decreases blood glucose levels, increases insulin sensitivity, and prevents dyslipidemia, to an extent which is greater than would be observed using the individual constituents alone. The inventors do not wish to be bound to any theory but believe that there is a synergy between the acetogenic fibres and the whey protein possibly due to the effects of the increase in tissue sensitivity to insulin and the stimulation of insulin secretion occurring simultaneously.

The term "dietary fibre" is generally understood to designate non-starch polysaccharides which cannot be digested by human enzymes and which pass intact through the stomach and small intestine arriving unchanged at the large intestine. In the large intestine, these fibres are fermented by the intestinal bacteria to produce gases, short chain fatty acids and esters of such acids, principally acetates, propionates and butyrates. The term " acetogenic fibre" is used herein to designate those dietary fibres which, upon fermentation in the large intestine produce predominantly acetic acid and acetates. Dietary fibres are generally classified in this way in the literature, alternatively, they may be fermented in vitro by batch techniques devised to simulate the conditions devised in the large intestine and the relative amounts of acetate, propionate and butyrate may be measured. When measured by this technique, an acetogenic fibre may be considered to be a fibre which, when fermented, produces at least 60% acetic acid/acetates. An alternative measure is the amount of acetate produced in which case an acetogenic fibre may be considered to be a fibre which, when fermented, produces at least about 550 μmoL of acetate per 100 mg of fibres in 24- hours in in vitro conditions with human inoculums. Examples of such fibres include lactulose, pectins such as citrus pectin, carrot pectin and apple pectin, soybean fibre, soy fibre, gum

Arabic and acacia gum. Soluble fibres and low-viscous fibres, that is, non-gel forming fibres having a low viscosity in aqueous solutions are preferred.

The acetogenic fiber may be incorporated in the present composition in an amount of from about 0.2 to 90 % by weight, preferably from 0.5 to 70 % by weight, more preferably 0.7 to 30 % by weight, even more preferably 5 to 25 % by weight, most preferred about 7% by weight, based on the total weight of the composition.

The term "mixture of free amino acids" designates a mixture comprising at least two, preferably at least four different amino acids, selected from the known natural occurring amino acids.

The intact whey protein or mixture of free amino acids may be present in the composition in an amount of from about 1 to 90 % by weight, preferably from 5 to 70 % by weight, more preferably 11 to 60 % by weight, even more preferably 21 to 40 % by weight and most preferably about 25 to 35 % by weight, on the basis of the total dry weight of the composition. Preferably the whey protein is sweet whey protein. Preferably the mixture of free amino acids consists of the individual amino acids which constitute an intact protein such as whey or casein in the respective quantities found in the intact protein although the content of one or more amino acids may be enriched, such as e.g. leucine, phenylalanine or tyrosine if desired.

It has been found that both intact whey proteins and mixtures of free amino acids have a particular effect after consumption by type 2 diabetes patients. According to the studies carried out both intact whey proteins and mixtures of free amino acids significantly increase the production and/or secretion of insulin, as determined by an increase in the maximal plasma concentration and bio-availability of pro-insulin, insulin and C-peptide. The C-peptide results from the formation of biological active insulin from pro-insulin and serves as an indicator showing how much insulin is produced in an individual. C-peptide is considered to represent the most accurate indicator for the production of insulin in ß-cells. In other words, intact whey proteins enhance post-prandial insulinemia and help to restore

the first phase of the insulin response of diabetic patients to a standard meal and the kinetics of post-prandial insulinemia provoked by dietary carbohydrates may thus be accurately modulated by such substances.

Preferably, both intact whey proteins and mixtures of free amino acids are used. This is because, in addition to their effect on post-prandial insulinemia, mixtures of free amino acids also exert a positive influence on blood glucose levels.

A composition for use in the present invention may comprise of from 1 to 90 % by weight, preferably from 5 to 70 % by weight, more preferably 11 to 60 % by weight, even more preferably 21 to 40 and most preferred of from about 25 to 35 % by weight of an amino acid mixture, on the basis of the total dry weight of the composition.

The composition with the ingredients as detailed above may therefore advantageously be used for treating, preventing and/or improving metabolic dysfunctions and/or conditions associated with Type 2 diabetes mellitus or insulin resistance, via e.g. enhancing post-prandial insulinemia, decreasing blood glucose levels, increasing insulin sensitivity, or preventing dyslipidemia.

The present composition and its use will also be of high interest for large parts of the population, which are not suffering from insulin resistance or Type 2 diabetes mellitus at present, but belong to a target group at risk to develop any of said disorders, either due to a high risk diet or genetic predisposition. Moreover, an enhancement of post-prandial insulinemia and/or an increase in insulin sensitivity is also highly interesting for other groups of persons, such as patients recovering from diseases or trauma leading to muscle depletion, exercising persons or elderly persons, since insulin is an anabolic hormone necessary for muscle mass maintenance and growth. High post-prandial insulinemia therefore promotes improving muscle mass accretion in exercising persons, is helpful for patients suffering from muscle depletion, and supports muscle maintenance in elderly persons. Depending on the target group to whom the composition will be administered, either needing a more pronounced improvement of insulin sensitivity, or a more intensive

enhancement of post-prandial insulinemia, and/or a more intensive decrease of blood glucose levels, etc., the amounts of acetogenic fibres, intact whey proteins and mixtures of free amino acids may be appropriately selected.

The composition as described above may of course also be used for the manufacture of a so called functional food product or a pharmaceutical composition.

During the first administrations of the composition according to the invention, one has to keep in mind that the acetogenic fibres have to be digested in the colon; therefore, it is preferable that the composition is absorbed between 3 and 7 hours before a meal, for example 4 hours. After a few administrations of the composition, we observe an increased insulin sensitivity, and in that second phase the composition may be consumed either together with a meal, in particular a meal containing carbohydrates, or shortly before or after such a meal, such as up to half an hour, or preferably, up to 10 minutes before or after such a meal. The composition may be taken separately or as a supplement to a meal.

During the first phase, when fibres have to be ingested a few hours before a meal, it is possible, if not desirable, to provide two compositions to the patient in order to obtain the best effect. The first composition, comprising acetogenic fibres, should be ingested between 3 and 7 hours before a meal, for example 4 hours. The second composition, comprising proteins having a rapid digestion rate and /or a mixture of free amino acids, should be ingested shortly before or after a meal.

Particularly good results may be achieved when providing at least 0.1 g of acetogenic fibers per kg body weight, more preferably between 0.1 to 1.5 g of acetogenic fibers per kg body weight, most preferably between 0.3 to 0.8 g of acetogenic fibers per kg body weight, even more preferably 0.5 g of acetogenic fibers per kg body weight in combination with at least 0.1 g of a mixture of free amino acids and/or at least 0.1 g intact whey proteins per kg body weight, more preferably in combination with 0.1 to 1 g of a mixture of free amino acids and/or 0.1 to 1 g of intact whey proteins per kg body weight, most preferably in combination with 0.5 to 0.8 g of a mixture of free amino acids and/or 0.5 to 0.8 g intact

whey proteins per kg body weight, e.g. during, before or after a standard meal, in particular a standard meal comprising carbohydrates. A standard meal is any meal comprising at least 150 kcal, more preferably at least 250 kcal.

The nutritional composition according to the present invention is preferably enterally administrable, such as in form of a powder, a liquid concentrate, or a ready-to-drink beverage. The composition can be directly consumed or admixed with various foodstuffs, in particular to ready-to-use snacks, dairy products or drinks, or used for the preparation of an oral or enteral nutritional composition or a fruit juice.

Depending on the desired application, i.e. whether e.g. mainly an improvement of insulin sensitivity and/or an enhancement of post-prandial insulinemia and/or a decrease of blood glucose levels, etc. is aimed at, the weight ratios of acetogenic fibres ("x"), whey proteins ("y") and free amino acids ("z") may vary e.g. between within the proportion x : y : z, wherein x and one of y and z are each selected between 0.1 and 10, preferably 0.5 and 5, more preferably 0.5 and 2, and the other one of y and z is selected between 0 and 10, preferably 0.1 and 5, more preferably 0.5 and 2. If both whey proteins and free amino acids are present, preferably there will be a greater quantity of whey proteins than free amino acids.

A composition according to the present invention may of course comprise other conventional ingredients, such as vitamins and minerals, other fibres both soluble and insoluble, fat, food additives etc..

In particular, vitamins and minerals may be present in an amount of between 30 % and 150 % of US RDA (US recommended (daily) dietary allowance) per daily dosage. Additionally, one or more food grade emulsifiers may be included in the nutritional composition, if desired, such as diacetyl tartaric acid esters of mono- and diglycerides, lecithin, and mono- or diglycerides or a mixture thereof. Similarly, suitable food-acceptable salts and/or stabilizers may also be included.

If a lipid source is included, it preferably comprises about 5% to 40 % of the energy (measured in calories) on the basis of the total energy of the composition; preferably, about 10 % to about 20 % of the energy. Any suitable fat or fat mixture may be used. Vegetable fat is particularly suitable, for example soy oil, palm oil, coconut oil, safflower oil, sunflower oil, corn oil, canola oil, lecithin and the like. Animal fat such as milk fat may also be added if desired.

If a carbohydrate source is included, it preferably comprises less than 10% by weight, preferably less than 5% by weight, more preferably less than 1% by weight of the composition. For some applications, such as e.g. ready-to-use beverages, compositions are advantageous which are essentially free from, or comprise less than 5% by weight of, mono-saccharides. If monosaccharides are present, glucose galactose and tagatose each preferably account for less than 40 % by weight, more preferably less than 10 % by weight, even more preferably less than 1 % by weight of the mono-saccharides. In other applications such as ready-to-use snacks, however, inclusion of a carbohydrate source may be advantageous, preferably in an amount to provide 1 to 70 %, more preferably 25 % to 45 % of the energy on basis of the total energy of the composition.

Non-caloric sweeteners, flavourings and food-acceptable colourings may also be included.

A particularly advantageous embodiment comprises a liquid composition such as a ready-to-use beverage based on fruit juice, vegetable juice, water, isotonic drinks, carbonated flavoured drinks, soft drinks, teas, coffees, dairy products, meat and/or vegetable soups or mixtures thereof, which may be supplemented with minerals, vitamins and/or carbonic acid, if desired. Beverages comprising fruit or vegetable juices provide additionally the advantage of comprising vitamins, minerals or even enzymes and provide an advantageous complementation of a nutritional composition according to the present invention. In particular, juices such as orange, apple, pineapple, grapefruit, lemon, lime, mango, passion fruit, elderberries, cranberries, currants, grape, tomato, carrot or combinations thereof may form the basis for a ready-to-use beverage.

A liquid composition may comprise from 11 to 97 % by weight, preferably from 21 to 80 % by weight, most preferably from 61 to 75 % by weight, of any of the before-mentioned juices, beverages, water or mixtures thereof, and from 3 to 89 % by weight, preferably from 20 to 79 % by weight, most preferably from 25 to 39 % by weight, of a composition according to the present invention, on basis of the total weight of the liquid preparation. When preparing a liquid composition, it will preferably include the acetogenic fibres, and in addition thereto, 1 to 20 % by weight whey proteins and/or 1 to 20 % by weight free amino acids, more preferably 5 to 12 % by weight whey proteins and/or 5 to 12 % by weight free amino acids.

Advantageously, a beverage according to the present invention delivers 1 to 150 kcal, preferably 21 to 100 kcal, more preferably 31 to 50 kcal per 100 g of liquid. For example, a beverage accompanying a standard meal may e.g. provide per dosage (i.e. per standard meal) 0.1 to 100 g, preferably 5 to 40 g acetogenic fibres, more preferably 10 to 30 g acetogenic fibres, even more preferably 20 g acetogenic fibres with 10 to 35 g of whey proteins and/or amino acid mixtures. If both whey proteins and amino acid mixtures are present, the ranges are preferably 1 to 100 g of one and 15 to 50 g of the other.

Of course, consumers may also prepare such a beverage by mixing a composition according to the present invention (e.g. according to instructions on the package) with a beverage of their choice.

Alternatively, a food product may be enriched with a composition according to the present invention. For example, a fermented milk, a yoghurt, a fresh cheese, a renneted milk, a confectionery bar, breakfast cereal flakes or bars, a drink, milk powder, soy-based product, non-milk fermented product or a nutritional supplement for clinical nutrition. Then, the amount of the composition added is preferably, at least 0.5 % by weight, more preferably 11 to 40 % by weight, on basis of the total weight of the food product.

Food products or beverages as detailed above, provide the advantage that they may be consumed shortly before, during, or shortly after a meal by a person, in particular from a

person suffering from Type 2 diabetes, and permit an easy solution for enhancing post-prandial insulinemia, restoring, at least partially, the first phase of the insulin response to a standard meal, decreasing blood glucose levels, increasing insulin sensitivity, and preventing dyslipidemia. Thus, compositions according to the present invention may be helpful in significantly increasing the quality of life of large groups of the population.

A composition according to the present invention may also be used for the preparation of an enteral nutritional formula, in particular for patients suffering from muscle depletion or for supporting muscle maintenance.

Compositions according to the present invention may be designed both for human consumption and for consumption by a companion animal, in particular for dogs and cats.

All before-mentioned products according to the present invention provide the advantage that they may be expected to be highly accepted by the consumers as they are formulated on basis of well-known nutritional components, which proved to be essentially free of undesired side-effects. Moreover, compositions according to the present invention are essentially free of unpleasant tastes and may be regularly, e.g. daily consumed.

The following examples are given by way of illustration only and should not be construed as limiting the subject-matter of the present application.

Example 1

A rat study was designed to determine the synergy effect(s) of acetogenic fibres and fast whey proteins enriched diets on metabolic parameters, in particular on fasting glycaemia evolution during a chronic diet treatment.

A longitudinal pre-clinical trial of 4 diet groups was designed. Eighty rats (of a diabetic model, Goto-Kakisaki) were tested during 8-week treatment alternatively with one of 4 diets, 20 rats per group. Diets were essentially made of either (group 1, control) casein protein + cellulose, (group 2) casein protein + acetogenic fibre (20% apple pectin: 80% acacia gum), (group 3) whey proteins + cellulose or (group 4, synergy) whey proteins + acetogenic fibre. Rats were sacrificed at the end for assessing organ weight. Venous blood was collected at the tail before starting and at the end of each treatment. Metabolic parameters were assessed using enzymatic kits. Glycaemia was determined in venous blood of 16-h-fasted rats using a glucometer (Bayer Ltd).

Food intakes were stable and identical between all groups, diets being isocaloric. The results showed that acetogenic fibres (group 2) increased fecal content ($P<0.05$) in caecum of rats compared to group 1 and 3. The synergy group showed an even higher content ($P<0.05$) in caecum of rats compared to all groups. Interestingly, the triglycerides (TG) in plasma were not different (Not Significant, NS) in group 1 and 3 (mean ± SD, 1.02 ± 0.29 and 1.10 ± 0.29 mmol/L respectively) but lower in the synergy group 4 ($P<0.05$ compared to group 1 and 3, 0.85 ± 0.22 mmol/L). TG in group 2 (0.93 ± 0.20 mmol/L) and 4 were not different (NS). Most interestingly, evolution of glycaemia was altered along with diabetes development of this rat model that has a natural increase in fasting glycaemia with age. There were no significant differences in the increasing evolution of venous blood glycaemia of 16-h-fasted rats between groups 1,2 and 3. However, a significant effect was observed in preventing increase in fasting glycaemia in rats submitted to the synergy treatment (group 4, see Table below).

Table: Effect of diets on venous glycaemia evolution of 16-h-fasted rats between end and start of treatment (1 rat failed in group 4).

Change in glycaemia (T8wk – To, mmol/L)						
Treatment	n	Mean	Standard Deviation	Min	Max	Difference: ANOVA + Least Significant Difference
Group 1	20	1.20	1.21	-0.78	3.56	Group 4 ($P < 0.05$)
Group 2	20	0.80	0.89	-1.11	2.22	NS
Group 3	20	1.16	1.27	-1.22	3.28	NS
Group 4	19	0.51	0.88	-094	2.33	Group 1 ($P < 0.05$)

In conclusion, the present pre-clinical trial showed beneficially that acetogenic fibres and whey proteins both included in the diet 8-wk-treatment prevented significantly from glycaemia increase compared to control diet treatment.

It should be understood that various changes and modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the present invention and without diminishing its attendant advantages. It is therefore intended that such changes and modifications will be covered by the appended claims.

Claims

1. Use of a composition comprising acetogenic fibres, and at least one compound selected from the group consisting of intact whey protein and mixtures of free amino acids, for the preparation of a nutritional and/or a pharmaceutical composition for treating, preventing and/or improving metabolic dysfunctions and conditions associated with Type 2 diabetes mellitus or insulin resistance.

2. The use of claim 1, wherein said acetogenic fibre is lactulose, citrus pectin, apple pectin, carrot pectin soybean fibre, soy fibre, acacia gum or gum Arabic or a mixture thereof.

3. The use of claim 1 or 2, wherein the amount of acetogenic fibers in the composition is in the range of from 0.2 to 90 % by weight, preferably from 0.5 to 50 % by weight, more preferably 0.7 to 30 % by weight, even more preferably 5 to 25 % by weight, most preferred about 7 % by weight, based on the total weight of the composition.

4. The use according to any preceding claim, wherein the whey protein is sweet whey protein.

5. The use according to any preceding claim, wherein the amount of intact whey proteins in the composition is in the range of from 1 to 90 % by weight, preferably from 5 to 70 % by weight, more preferably 11 to 50 % by weight, even more preferably 21 to 40 % by weight, most preferred about 25 to 35 % by weight, based on the total dry weight of the composition.

6. The use according to any preceding claim, wherein the composition comprises both intact whey proteins and a mixture of free amino acids.

7. The use according to any preceding claim, wherein the amount of the mixture of amino acids in the composition is in the range of from 1 to 90 % by weight, preferably from 5 to 70 % by weight, more preferably 11 to 50 % by weight, even more preferably 21 to 40 % by weight, most preferred about 25 to 35 % by weight, based on the total dry weight of the composition.

8. The use according to any preceding claim wherein the individual amino acids are selected in both type and quantity to correspond with the amino acids which constitute an intact dietary protein.

9. The use according to any preceding claim, for enhancing post-prandial insulinemia, stimulating insulin production, increasing insulin sensitivity, preventing dyslipidemia, preventing fasting glycaemia increase and/or decreasing blood glucose levels.

10. Nutritional or pharmaceutical composition comprising acetogenic fibers, intact whey proteins and a mixture of free amino acids, each in an amount in the range of from about 1 to 90 % by weight, preferably from 5 to 70 % by weight, more preferably 11 to 50 % by weight, even more preferably 21 to 40 % by weight, most preferred about 25 to 35 % by weight, based on the total dry weight of the composition.

11. The composition according to claim 9, wherein said acetogenic fiber is lactulose, citrus pectin, apple pectin, carrot pectin soybean fibre, soy fibre, acacia gum or gum Arabic or a mixture thereof.

12. The composition according to claim 9 or 10, wherein the intact whey protein is sweet whey protein.

13. The composition according to any of claims 9 to 12, wherein the individual amino acids are selected in both type and quantity to correspond with the amino acids which constitute an intact dietary protein.

14. A liquid nutritional composition comprising 11 to 97 % by weight of a liquid selected from the group consisting of fruit juice, vegetable juice, water, isotonic drinks, carbonated flavored drinks, soft drinks, teas, coffees, dairy products, meat and/or vegetable soups or mixtures thereof, and 3 to 89 % by weight of a composition according to claims 10 to 13, all on the basis of the total weight of the liquid composition.

15. A method for treating, preventing and/or improving metabolic dysfunctions or conditions associated with Type 2 diabetes mellitus or insulin resistance which comprises administering an effective amount of a composition comprising acetogenic fibres, and at least one compound selected from the group consisting of intact whey proteins and mixtures of free amino acids.

16. A method according to claim 15 wherein the composition comprises both intact whey proteins and mixtures of free amino acids.

17. The method of claim 16 in which intact whey proteins are administered in an amount of 0.5 to 0.8 g intact whey proteins per kg body weight the acetogenic fibres are administered in an amount of from 0.3 to 0.8 g per kg body weight and the mixture of free amino acids is administered in an amount of 0.5 to 0.8 g intact whey proteins per kg body weight.

18. The method of any one of claims 15 to 17 wherein the acetogenic fibres and intact whey proteins are co-administered.

19. The method of any one of claims 15 to 17 wherein the acetogenic fibres and intact whey proteins are administered sequentially, the acetogenic fibres being administered 3 to 7 hours before a meal and the intact whey proteins being administered at or immediately before the meal.